* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Jun 13	Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN
NEWS 40	May 19	Simultaneous left and right truncation added to WSCA
NEWS 41	May 19	RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 42	Jun 06	Simultaneous left and right truncation added to CBNB
NEWS 43	Jun 06	PASCAL enhanced with additional data
NEWS 44	Jun 20	2003 edition of the FSTA Thesaurus is now available
NEWS 45	Jun 25	HSDB has been reloaded

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT

STN Columbus

MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 10:26:19 ON 09 JUL 2003

=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 10:26:42 ON 09 JUL 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 8 JUL 2003 HIGHEST RN 544651-49-2
DICTIONARY FILE UPDATES: 8 JUL 2003 HIGHEST RN 544651-49-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

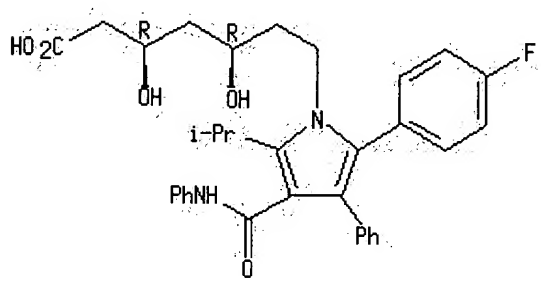
=> s atorvastatin/cn
L1 1 ATORVASTATIN/CN

=> d

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 134523-00-5 REGISTRY
CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, (βR,δR)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, [R-(R*,R*)]-
OTHER NAMES:
CN (βR,δR)-2-(p-Fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid
CN **Atorvastatin**
CN Cardyl
FS STEREOSEARCH
MF C33 H35 F N2 O5
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IPA, MEDLINE, MRCK*, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

761 REFERENCES IN FILE CA (1957 TO DATE)
22 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
788 REFERENCES IN FILE CAPLUS (1957 TO DATE)

=> s 134523-00-5/rn or 134523-00-5/crn
1 134523-00-5/RN
17 134523-00-5/CRN
L2 18 134523-00-5/RN OR 134523-00-5/CRN

=> fil hcapl

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	6.70	6.91

FILE 'HCAPLUS' ENTERED AT 10:27:48 ON 09 JUL 2003

FILE COVERS 1907 - 9 Jul 2003 VOL 139 ISS 2
FILE LAST UPDATED: 8 Jul 2003 (20030708/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l2
L3 875 L2

=> s angiogenes?
L4 17678 ANGIOGENES?

=> s l3 and l4
L5 14 L3 AND L4

=> d ibib abs 11-14

L5 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 2001:884254 HCAPLUS
DOCUMENT NUMBER: 136:160858
TITLE: Top 200 medicines: can new actions be discovered through computer-aided prediction?
AUTHOR(S): Poroikov, V.; Akimov, D.; Shabelnikova, E.; Filimonov, D.
CORPORATE SOURCE: Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, Moscow, 119832, Russia
SOURCE: SAR and QSAR in Environmental Research (2001), 12(4), 327-344
CODEN: SQERED; ISSN: 1062-936X
PUBLISHER: Gordon & Breach Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Computer-aided prediction of the biol. activity spectra by the program PASS was applied to a set of 130 pharmaceuticals from the list of the Top 200 medicines. The known pharmacol. effects were found in the predicted activity spectra in 93.2% of cases. Addnl., the probability of some supplementary effects was also predicted to be significant, including **angiogenesis** inhibition, bone formation stimulation, possible use in cognition disorders treatment, multiple sclerosis treatment, etc. These predictions, if confirmed exptl., may become a cause for a new application of pharmaceuticals from the Top 200 list. Most of known side and toxic effects were also predicted by PASS. PASS predictions at earlier R & D stages may thus provide a basis for finding new "leads" among already launched drugs and may help direct more attention to those particular effects of pharmaceuticals in clin. use which become apparent only in a small part of the population and require addnl. precautions.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2001:862942 HCAPLUS
DOCUMENT NUMBER: 136:145009
TITLE: Hsp90 and caveolin are key targets for the proangiogenic nitric oxide-mediated effects of statins
AUTHOR(S): Brouet, Agnes; Sonveaux, Pierre; Dessy, Chantal; Moniotte, Stephane; Balligand, Jean-Luc; Feron, Olivier
CORPORATE SOURCE: Department of Medicine, University of Louvain Medical School, Brussels, B-1200, Belg.
SOURCE: Circulation Research (2001), 89(10), 866-873
CODEN: CIRUAL; ISSN: 0009-7330
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 3-Hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors or statins exert direct beneficial effects on the endothelium in part through an increase in nitric oxide (NO) prodn. Here, we examd. whether posttranslational modifications of the endothelial NO synthase (eNOS) could account for the proangiogenic effects of statins. We used endothelial cells (ECs) isolated from cardiac microvasculature, aorta, and umbilical veins, as well as dissected microvessels and aortic rings, that were cultured on reconstituted basement membrane matrix (Matrigel). Tube or precapillary formation was evaluated after statin treatment, in parallel with immunoblotting and immunopptn. expts. Atorvastatin stimulated NO-dependent **angiogenesis** from both isolated and outgrowing (vessel-derived) ECs, independently of changes in eNOS expression. We found that in macro- but not microvascular ECs, atorvastatin stabilized tube formation through a decrease in caveolin abundance and its inhibitory interaction with eNOS. We also identified the chaperone protein hsp90 as a key target for the proangiogenic effects of statins. Using geldanamycin, an inhibitor of hsp90 function, and overexpression of recombinant hsp90, we documented that the statin-induced phosphorylation of eNOS on-Ser1177 was directly dependent on the ability of hsp90 to recruit Akt in the eNOS complex. Finally, we showed that statin promoted the tyrosine phosphorylation of hsp90 and the direct interaction of hsp90 with Akt, which further potentiated the NO-dependent angiogenic processes. Our study provides new mechanistic insights into the NO-mediated angiogenic effects of statins and underscores the potential of these drugs and other modulators of hsp90 and caveolin abundance to promote neovascularization in disease states assocd. or not with atherosclerosis.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2001:538011 HCAPLUS
DOCUMENT NUMBER: 136:256932
TITLE: Increase in circulating endothelial progenitor cells by statin therapy in patients with stable coronary artery disease
AUTHOR(S): Vasa, Mariuca; Fichtlscherer, Stephan; Adler, Klaudia; Aicher, Alexandra; Martin, Hans; Zeiher, Andreas M.; Dimmeler, Stefanie
CORPORATE SOURCE: Division of Molecular Cardiology, Department of Internal Medicine IV, University of Frankfurt, Frankfurt, Germany
SOURCE: Circulation (2001), 103(24), 2885-2890
CODEN: CIRCAZ; ISSN: 0009-7322

PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: Therapeutic neovascularization may constitute an important strategy to salvage tissue from crit. ischemia. Circulating bone marrow-derived endothelial progenitor cells (EPCs) were shown to augment the neovascularization of ischemic tissue. In addn. to lipid-lowering activity, hydroxymethyl glutaryl CoA reductase inhibitors (statins) reportedly promote the neovascularization of ischemic tissue in normocholesterolemic animals. Methods and Results: Fifteen patients with angiog. documented stable coronary artery disease (CAD) were prospectively treated with 40 mg of atorvastatin per day for 4 wk. Before and weekly after the initiation of statin therapy, EPCs were isolated from peripheral blood and counted. In addn., the no. of hematopoietic precursor cells pos. for CD34, CD133, and CD34/kinase insert domain receptor was analyzed. Statin treatment of patients with stable CAD was assocd. with an ≈1.5-fold increase in the no. of circulating EPCs by I week after initiation of treatment; this was followed by sustained increased levels to ≈3-fold throughout the 4-wk study period. Moreover, the no. of CD34/kinase insert domain receptor-pos. hematopoietic progenitor cells was significantly augmented after 4 wk of therapy. Atorvastatin treatment increased the further functional activity of EPCs, as assessed by their migratory capacity. Conclusion: The results of the present study define a novel mechanism of action of statin treatment in patients with stable CAD: the augmentation of circulating EPCs with enhanced functional activity. Given the well-established role of EPCs of participating in repair after ischemic injury, stimulation of EPCs by statins may contribute to the clin. benefit of statin therapy in patients with CAD.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 2000:814293 HCAPLUS
DOCUMENT NUMBER: 133:344620
TITLE: Use of HMG-CoA reductase inhibitors in the prevention of diseases whose pathogenesis is dependent on neovascularization
INVENTOR(S): Galper, Jonas B.; Kong, Dequan
PATENT ASSIGNEE(S): The Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067737	A2	20001116	WO 2000-US12309	20000505

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-132964P A2 19990507

AB HMG-CoA reductase inhibitors have a well-known mechanism in controlling cholesterol metab. HMG-CoA reductase inhibitors also have a less well-known effect on gene expression. The invention provides a new use for HMG-CoA reductase inhibitors in the treatment of diseases whose pathogenesis is dependent on neovascularization. HMG-CoA reductase inhibitors are administered at anti-angiogenic therapeutic doses for the treatment of primary and metastatic tumors, inflammatory processes involving new vessel formation, diabetic retinopathy, rheumatoid arthritis, and atherosclerosis. HMG-CoA reductase inhibitors affect the expression of genes through interference with the function of small GTP-binding proteins (e.g. Rho). Because of the low incidence of side effects with these agents, HMG-CoA reductase inhibitors could also be taken prophylactically to prevent the development of diseases in which the pathogenesis is caused by neovascularization.

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=> s atheroscler? or arterioscler?
         37950 ATHEROSCLER?
         10226 ARTERIOSCLER?
L6       43657 ATHEROSCLER? OR ARTERIOSCLER?

=> s l6 and l3
L7         191 L6 AND L3

=> s l3 (S) l6
L8          34 L3 (S) L6

=> d ibib abs 31-34

L8   ANSWER 31 OF 34  HCAPLUS  COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER:        1998:625982  HCAPLUS
DOCUMENT NUMBER:         130:20459
TITLE:                   Treating patients with documented atherosclerosis to
                         national cholesterol education program-recommended
                         low-density-lipoprotein cholesterol goals with
                         atorvastatin, fluvastatin, lovastatin and simvastatin
AUTHOR(S):               Brown, Alan S.; Bakker-Arkema, Rebecca G.; Yellen,
                         Laurence; Henley, Robert W., Jr.; Guthrie, Richard;
                         Campbell, Cam F.; Koren, Michael; Woo, William;
                         McLain, Richard; Black, Donald M.
CORPORATE SOURCE:        Midwest Heart Research Foundation, Naperville, IL, USA
SOURCE:                  Journal of the American College of Cardiology (1998),
                         32(3), 665-672
                         CODEN: JACCDI; ISSN: 0735-1097
PUBLISHER:               Elsevier Science Inc.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
```

AB This study compared the efficacy and safety of atorvastatin, fluvastatin, lovastatin, and simvastatin in patients with documented atherosclerosis treated to U.S. National Cholesterol Education Program (NCEP) recommended low-d.-lipoprotein (LDL) cholesterol concn. (≤100 mg/dL [2.59 mmol/L]). For patients with advanced atherosclerosis, NCEP recommends lipid-lowering drug therapy if LDL cholesterol remains ≥130 mg/dL (3.36 mmol/L). A total of 318 men or women with documented atherosclerosis and LDL cholesterol ≥130 mg/dL (3.36 mmol/L) and ≤250 mg/dL (6.5 mmol/L), and triglycerides ≤400 mg/dL (4.5 mmol/L) participated in this 54-wk, multicenter, open-label, randomized, parallel-group, active-controlled, treat-to-target study. Patients were

titrated at 12-wk intervals until the LDL cholesterol goal was reached. No. of patients reaching target LDL cholesterol levels and dose to reach target were evaluated. At the starting doses, atorvastatin 10 mg produced significantly greater decreases ($p < 0.05$) in plasma LDL cholesterol than the other treatments. Subsequently, the percentage of patients reaching goal at the starting dose was 32% for atorvastatin, 1% for fluvastatin, 10% for lovastatin and 22% for simvastatin. Atorvastatin-treated patients required a lower median dose than other treatments. Median doses at week 54 with the last available visit carried forward were atorvastatin 20 mg/day, fluvastatin 40 mg/day + colestipol 20 g/day, lovastatin 80 mg/day, simvastatin 40 mg/day. A significantly greater no. ($p < 0.05$) of patients with confirmed atherosclerosis treated with atorvastatin reached the target LDL cholesterol concn. at the starting dose than patients treated with fluvastatin or lovastatin, and significantly fewer ($p < 0.05$) patients treated with atorvastatin required combination therapy with colestipol to achieve target LDL cholesterol concns. than all other statins tested.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 1998:509102 HCAPLUS
DOCUMENT NUMBER: 129:153237
TITLE: Method for treating atherosclerosis with an MPT inhibitor and cholesterol-lowering drugs
INVENTOR(S): Behounek, Bruce D.; Mcgovern, Mark E.; Belder, Rene
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9831366	A1	19980723	WO 1998-US524	19980112
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9862397	A1	19980807	AU 1998-62397	19980112
AU 727895	B2	20010104		
EP 989852	A1	20000405	EP 1998-904548	19980112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001508795	T2	20010703	JP 1998-534460	19980112

PRIORITY APPLN. INFO.: US 1997-35592P P 19970117
WO 1998-US524 W 19980112

OTHER SOURCE(S): MARPAT 129:153237

AB A method is provided for preventing or reducing the risk of onset of a cardiovascular event by administering an MTP (microsomal triglyceride transfer protein) inhibitor alone or in combination with another cholesterol lowering drug such as an HMG CoA reductase inhibitor such as pravastatin, to a patient who may or may not have one or more risk factors

for a coronary and/or cerebrovascular event such as hypercholesterolemia. Capsules were prepd. contg. the MTP inhibitor BMS 201,038 and tablets were prepd. contg. cholesterol inhibitors and BMS 201,038 or BMS 201,238.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 1997:178769 HCAPLUS
DOCUMENT NUMBER: 126:176899
TITLE: Synergistic combination comprising an insulin sensitizer and a HMG-CoA reductase inhibitor for treating arteriosclerosis
INVENTOR(S): Tsujita, Yoshio; Horikoshi, Hiroyoshi; Shiomi, Masashi; Ito, Takashi
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 753298	A1	19970115	EP 1996-304924	19960703
EP 753298	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CA 2180296	AA	19970104	CA 1996-2180296	19960702
NO 9602784	A	19970106	NO 1996-2784	19960702
AU 9656261	A1	19970116	AU 1996-56261	19960702
AU 706628	B2	19990617		
JP 09071540	A2	19970318	JP 1996-172137	19960702
US 5798375	A	19980825	US 1996-676090	19960702
IL 118778	A1	19990714	IL 1996-118778	19960702
RU 2158607	C2	20001110	RU 1996-112769	19960702
TW 474809	B	20020201	TW 1996-85107984	19960702
ZA 9605650	A	19970127	ZA 1996-5650	19960703
CN 1148492	A	19970430	CN 1996-112170	19960703
CN 1089584	B	20020828		
CZ 286832	B6	20000712	CZ 1996-1982	19960703
AT 209046	E	20011215	AT 1996-304924	19960703
ES 2165474	T3	20020316	ES 1996-304924	19960703
US 6159997	A	20001212	US 1998-61446	19980416
HK 1011928	A1	20020628	HK 1998-113080	19981210

PRIORITY APPLN. INFO.: JP 1995-167291 A 19950703
US 1996-676090 A3 19960702

AB A combination of 1 or more HMG-CoAreductase inhibitors (e.g., pravastatin, lovastatin, simvastatin, fluvastatin, rivastatin or atorvastatin) with 1 or more insulin sensitizers (e.g., troglitazone, pioglitazone, englitazone, BRL-49653, 5-(4-{2-[1-(4-2'-pyridylphenyl)ethylideneaminooxy] ethoxy)benzyl}thiazolidine-2,4-dione) exhibits a synergistic effect and is better at prevention and/or treatment of arteriosclerosis and/or xanthoma than is either of the components of the combination alone. Thus, pravastatin sodium 0.5, troglitazone 20, Crospovidone 1.5, and Na lauryl sulfate 0.2 g were blended and the mixt. was divided among 100 capsules, each contg. 5 mg pravastatin sodium and 200 mg troglitazone. The prepn. of some thiazolidine-2,4-diones is reported.

L8 ANSWER 34 OF 34 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 1996:431460 HCAPLUS
DOCUMENT NUMBER: 125:76399
TITLE: Combination of a cholesterol absorption inhibitor and a cholesterol synthesis inhibitor for treatment of hypercholesterolemia and atherosclerosis
INVENTOR(S): Morehouse, Lee A.
PATENT ASSIGNEE(S): Morehouse, Lee, A., USA
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9609827	A2	19960404	WO 1995-IB447	19950607
WO 9609827	A3	19960523		
W: AU, CA, CN, CZ, FI, HU, JP, KR, MX, NO, NZ, PL, RU, SI, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2200436	AA	19960404	CA 1995-2200436	19950607
AU 9524532	A1	19960419	AU 1995-24532	19950607
EP 782451	A1	19970709	EP 1995-918721	19950607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 09511753	T2	19971125	JP 1995-511549	19950607
BR 9504072	A	19960730	BR 1995-4072	19950919
ZA 9507879	A	19970319	ZA 1995-7879	19950919
US 5807834	A	19980915	US 1997-793802	19970318
FI 9701151	A	19970319	FI 1997-1151	19970319

PRIORITY APPLN. INFO.: US 1994-308908 A 19940920
WO 1995-IB447 W 19950607
OTHER SOURCE(S): MARPAT 125:76399
AB Pharmaceutical combination compns. are disclosed which include certain cholesterol absorption inhibitors and cholesterol synthesis inhibitors. The compns. are useful for the treatment of hypercholesterolemia and atherosclerosis. The effect of e.g. tigogenin cellobioside and lovastatin on plasma cholesterol levels and hepatic HMG-CoA reductase activity in hamsters is reported.

=> d ibib abs 26-30

L8 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 2000:189750 HCAPLUS
DOCUMENT NUMBER: 132:343112
TITLE: Regression of poloxamer 407-induced atherosclerotic lesions in C57BL/6 mice using atorvastatin
AUTHOR(S): Johnston, T. P.; Baker, J. C.; Hall, D.; Jamal, S.; Palmer, W. K.; Emeson, E. E.
CORPORATE SOURCE: School of Pharmacy, Division of Pharmaceutical Sciences, University of Missouri, Kansas City, MO, USA
SOURCE: Atherosclerosis (Shannon, Ireland) (2000), 149(2), 303-313
CODEN: ATHSBL; ISSN: 0021-9150
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB HMG-CoA reductase inhibitor drugs or 'statins' have been shown to effectively reduce plasma total cholesterol (CHOL), CHOL assocd. with low-d.-lipoprotein (LDL), and triglycerides (TG). In addn., slight elevations in HDL-CHOL are also typically obsd. Poloxamer 407 (P-407), a nonionic surfactant, effectively elevates both plasma CHOL and esp. TG in a dose-controlled fashion and results in formation of atherosclerotic lesions in the aortas of C57BL/6 mice without the requirement of dietary cholic acid [1,2]. The purpose of the present study was to assess whether a typical statin, namely atorvastatin (Lipitor®) would significantly reduce P-407-induced hypercholesterolemia and hypertriglyceridemia as well as cause regression of atherosclerotic lesions resulting from administration of P-407 to C57BL/6 mice. C57BL/6 mice in the present study were treated with either normal saline (C, controls), 0.5 g/kg of P-407 (P), or a high-fat, high-cholesterol, cholate-contg. diet (HF) for 120 days. Mice in all groups were then equally and randomly divided and treated with either atorvastatin or saline for an addnl. 120 days. Beginning at Day 121 and using mice in groups P and HF as an example, one-fourth of the mice in each group received 20 mg/kg per day of atorvastatin with either concomitant HF feeding or P-407 administration ('progression' treatment groups), one-fourth received 20 mg/kg per day of atorvastatin following cessation of HF feeding or P-407 administration, one-fourth received saline (placebo) with either simultaneous HF feeding or P-407 administration ('progression' placebo groups), and one-fourth received saline (placebo) following cessation of HF feeding or P-407 administration. Total plasma CHOL was significantly ($P<0.01$) lower for mice in groups P and HF when administered atorvastatin relative to saline, but remained significantly ($P<0.05$) elevated compared to total plasma CHOL of C mice. With discontinuation of either P-407 administration or HF feeding, total plasma CHOL declined rapidly in both P and HF mice with atorvastatin-treated mice generally demonstrating lower plasma CHOL concns. relative to saline-treated mice. Total plasma TG was significantly ($P<0.01$) lower for mice in group P administered atorvastatin relative to saline, but remained significantly ($P<0.05$) elevated compared to plasma TG of C mice. With discontinuation of P-407 administration, total plasma TG declined rapidly in P mice with atorvastatin-treated mice typically demonstrating lower plasma TG concns. relative to saline-treated P mice. Aortas of mice treated with 20 mg/kg per day of atorvastatin in both groups P and HF, whether maintained on the HF-diet or treated with P-407 from Day 120 to 240 or whether each treatment was terminated at Day 120, revealed no presence of atherosclerotic lesions relative to saline-treated mice and were indistinguishable from aortas retrieved from C mice. Atorvastatin at a dose of 20 mg/kg per day not only significantly reduced the plasma CHOL and TG concns., but also resulted in regression of atherosclerotic lesions induced in C57BL/6 mice by administration of P-407 or ingestion of a HF-diet contg. cholic acid.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2000:93323 HCAPLUS
DOCUMENT NUMBER: 133:52
TITLE: The evolving role of statins in the management of atherosclerosis
AUTHOR(S): Vaughan, Carl J.; Gotto, Antonio M., Jr.; Basson, Craig T.
CORPORATE SOURCE: Division of Cardiology, Department of Medicine, Weill Medical College of Cornell University, The New York Presbyterian Hospital, New York, NY, 10021, USA
SOURCE: Journal of the American College of Cardiology (2000),

35(1), 1-10
CODEN: JACCDI; ISSN: 0735-1097
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 88 refs. Significant advances in the management of cardiovascular disease have been made possible by the development of 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase inhibitors-"statins.". Initial studies explored the impact of statin therapy on coronary artery disease (CAD) progression and regression. Although the angiog. changes were small, assocd. clin. responses appeared significant. Subsequent large prospective placebo-controlled clin. trials with statins demonstrated benefit in the secondary and primary prevention of CAD in subjects with elevated cholesterol levels. More recently, the efficacy of statins has been extended to the primary prevention of CAD in subjects with av. cholesterol levels. Recent studies also suggest that statins have benefits beyond the coronary vascular bed and are capable of reducing ischemic stroke risk by approx. one-third in patients with evidence of vascular disease. In addn. to lowering low-d. lipoprotein (LDL) cholesterol, statin therapy appears to exhibit pleiotropic effects on many components of atherosclerosis including plaque thrombogenicity, cellular migration, endothelial function and thrombotic tendency. Growing clin. and exptl. evidence indicates that the beneficial actions of statins occur rapidly and yield potentially clin. important anti-ischemic effects as early as one month after commencement of therapy. Future investigations are warranted to det. threshold LDL values in primary prevention studies, and to elucidate effects of statins other than LDL lowering. Finally, given the rapid and protean effects of statins on determinants of platelet reactivity, coagulation, and endothelial function, further research may establish a role for statin therapy in acute coronary syndromes.

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2000:4636 HCAPLUS
DOCUMENT NUMBER: 132:30628
TITLE: Efficacy of vitamin E compared with either simvastatin or atorvastatin in preventing the progression of atherosclerosis in homozygous familial hypercholesterolemia
AUTHOR(S): Raal, Frederick J.; Pilcher, Gillian J.; Veller, Martin G.; Kotze, Maritha J.; Joffe, Barry I.
CORPORATE SOURCE: The Carbohydrate and Lipid Metabolism Research Group, Department of Medicine, and The Vascular Unit, Department of Surgery, University of the Witwatersrand, Johannesburg, 2193, S. Afr.
SOURCE: American Journal of Cardiology (1999), 84(11), 1344-1346
CODEN: AJCDAG; ISSN: 0002-9149
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study compared the efficacy of antioxidant (vitamin E) with lipid-lowering (statin) therapy in patients with homozygous familial hypercholesterolemia (HFH) because these patients are known to have severe, accelerated atherosclerosis. Redn. of LDL cholesterol by high-dose simvastatin or atorvastatin was more effective than vitamin E in delaying progression of atherosclerosis in HFH patients with severe hypercholesterolemia.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 1999:464665 HCAPLUS
DOCUMENT NUMBER: 131:295408
TITLE: Nitric oxide synthase II (NOS II) gene expression correlates with atherosclerotic intimal thickening. Preventive effects of HMG-CoA reductase inhibitors
AUTHOR(S): Alfon, Jose; Guasch, Joan F.; Berrozpe, Maria; Badimon, Lina
CORPORATE SOURCE: CSIC-HSCSP-UAB, Cardiovascular Research Center, Barcelona, 08034, Spain
SOURCE: Atherosclerosis (Shannon, Ireland) (1999), 145(2), 325-331
CODEN: ATHSBL; ISSN: 0021-9150
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB HMG-CoA reductase inhibitors have been shown to be effective in primary and secondary prevention of coronary heart disease. Their mechanism of action is attributed to their cholesterol lowering activity but recent results seem to indicate addnl. effects related to the modulation of other processes that regulate the presentation of vascular diseases. Our objective has been to study the effects of atorvastatin and simvastatin, two HMG-CoA reductase inhibitors, on lesion compn. and expression of genes involved in lesion development in a diet-induced atherosclerotic rabbit model. Both HMG-CoA reductase inhibitors were administered at identical doses of 2.5 mg/kg per day with the hyperlipemic diet for 10 wk. Both statins significantly prevented the diet-induced increase in cholesterol levels. Relative lesion compn. in fibrinogen, macrophages and smooth muscle cells was unaltered by the treatment although lesion size was reduced; therefore, both HMG-CoA reductase inhibitors reduced total amts. of fibrinogen, macrophages and smooth muscle cells (simvastatin, $P<0.05$). NOS II gene expression was pos. and significantly correlated with lesion size and inversely correlated with HDL plasma levels. NOS II expression was markedly downregulated in simvastatin treated animals while MCP-1 was unaltered. Therefore, HMG-CoA reductase inhibition seems to interfere with atherosclerotic lesion development by reducing intimal thickening development and the expression of the cytotoxic NOS II.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 1999:1203 HCAPLUS
DOCUMENT NUMBER: 130:218023
TITLE: HMG-CoA reductase inhibition by atorvastatin reduces neointimal inflammation in a rabbit model of atherosclerosis
AUTHOR(S): Bustos, Carmen; Hernandez-Presa, Miguel A.; Ortego, Monica; Tunon, Jose; Ortega, Luis; Perez, Fernando; Diaz, Cristina; Hernandez, Gonzalo; Egido, Jesus
CORPORATE SOURCE: Fundacion Jimenez Diaz, Universidad Autonoma, Madrid, 28040, Spain
SOURCE: Journal of the American College of Cardiology (1998), 32(7), 2057-2064
CODEN: JACCDI; ISSN: 0735-1097
PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors studied the effect of the 3-hydroxy-3-methylglutaryl CoA (HMG-CoA)-reductase inhibitor atorvastatin on the potential mechanisms involved in the recruitment of monocytic cells into the vessel wall. Inhibitors of HMG-CoA-reductase reduce cardiovascular mortality. Most ischemic events are secondary to disruption of atherosclerotic plaques highly infiltrated by macrophages. Atherosclerosis was induced in the femoral arteries of rabbits by endothelial damage and atherogenic diet for 4 wk. Then, animals were switched to std. chow and randomized to receive either no treatment or atorvastatin (5 mg/kg/d) and killed after 4 wk. Atorvastatin induced a significant redn. in serum lipids and in lesion size. Arterial macrophage infiltration was abolished by the treatment, and monocyte chemoattractant protein-1 (MCP-1) was significantly diminished in the neointima and in the media. Nuclear factor kappa-B (NF-κB) was activated in the 60% of the lesions, both in macrophages and vascular smooth muscle cells (VSMC), of the untreated group while only in 30% of the atorvastatin group. NF-κB activity was also lower in the uninjured aorta and liver of treated compared with untreated rabbits. In cultured VSMC, MCP-1 expression and NF-κB activity induced by tumor necrosis factor alpha were down-regulated by atorvastatin. In a rabbit atherosclerosis model, atorvastatin diminishes the neointimal inflammation, and this could contribute to the stabilization of the atherosclerotic plaque. This may be an addnl. explanation for the redn. of acute ischemic events in patients treated with statins.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s HMG-CoA
          7803 HMG
            91 HMGS
          7822 HMG
                 (HMG OR HMGS)
         35746 COA
           826 COAS
         35912 COA
                 (COA OR COAS)
L9        4737 HMG-COA
                 (HMG(W)COA)

=> s l9 and l4
L10         54 L9 AND L4

=> d ibib abs 50-54
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L10 ANSWER 50 OF 54 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 2001:70709 HCAPLUS
DOCUMENT NUMBER: 137:150025
TITLE: The **HMG-CoA** reductase inhibitor simvastatin activates the protein kinase Akt and promotes **angiogenesis** in normocholesterolemic animals. [Erratum to document cited in CA133:329364]
AUTHOR(S): Kureishi, Yasuko; Luo, Zhengyu; Shiojima, Ichiro; Bialik, Ann; Fulton, David; Lefer, David J.; Sessa, William C.; Walsh, Kenneth
CORPORATE SOURCE: Div. Cardiovascular Res., St. Elizabeth's Med. Center, Boston, MA, 02136, USA

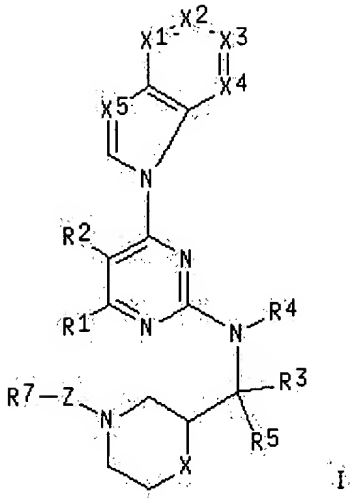
SOURCE: Nature Medicine (New York) (2001), 7(1), 129
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The correct labeling for Fig. 3c on page 1006 is given.

L10 ANSWER 51 OF 54 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 2001:12274 HCAPLUS
DOCUMENT NUMBER: 134:86272
TITLE: Preparation of pyrimidine derivatives as Src-family protein tyrosine kinase inhibitor compounds
INVENTOR(S): Hunt, Julianne A.; Mills, Sander G.; Sinclair, Peter J.; Zaller, Dennis M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 181 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000214	A1	20010104	WO 2000-US17472	20000626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6316444	B1	20011113	US 2000-603699	20000626
EP 1194152	A1	20020410	EP 2000-944858	20000626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003503354	T2	20030128	JP 2001-505923	20000626

PRIORITY APPLN. INFO.: US 1999-141597P P 19990630
WO 2000-US17472 W 20000626

OTHER SOURCE(S): MARPAT 134:86272
GI



I

AB What are claimed are pyrimidine compds. (shown as I), or their pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers, and pharmaceutical compns. including the same and their use as inhibitors of tyrosine kinase enzymes and consequently their use in the prophylaxis and treatment of protein tyrosine kinase-assocd. disorders, such as immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to play a role, such as cancer, **angiogenesis**, atherosclerosis, graft rejection, rheumatoid arthritis and psoriasis. In I, R1, R2 = independently H, halo, OH, SH, CN, NO2, alkyl, alkoxy, acyloxy, alkoxycarbonyloxy, carbamoyloxy, alkylthio, sulfinyl, sulfonyl, acyl, alkoxycarbonyl, carbamoyl, amino, acylamino, alkoxycarbonylamino, ureido, sulfamoyl, sulfonylamino, or R1 and R2 can join together to form a fused methylenedioxy ring or a fused 6-membered arom. ring; terms such as 'alkyl' here and below are further defined in the claims. R3, R5 = independently H, C1-C6-alkyl unsubstituted or substituted with 1-3 substituents, aryl (Ph or naphthyl unsubstituted or substituted with 1-3 substituents), or R3 and R5 taken together can represent :O. R4 = H, C1-C6-alkyl, C1-C6-alkoxyl, or R4 and X can join together to form a 5- or 6-membered ring with substituted methylene or ethylene. X1, X2, X3, X4 in -X1:X2-X3:X4- are substituted CH or N where 0-2 of X1, X2, X3, X4 are N. X5 = N, CH. R7 = H, alkyl, alkoxy, amino. X = O, S, SO, SO2, imino. Z = C:O, SO2, substituted P(:O)(OH) or a single bond. 44 Example prepns. are given, but no preparative method is claimed and no data relating to the usefulness of the compds. are given.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 52 OF 54 HCAPLUS COPYRIGHT 2003 ACS
Full Text

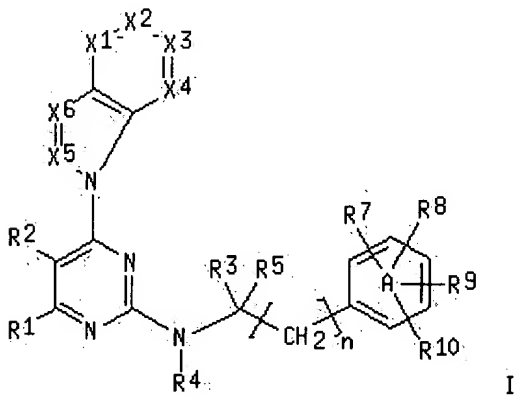
ACCESSION NUMBER: 2001:12273 HCAPLUS
DOCUMENT NUMBER: 134:86271
TITLE: Preparation of pyrimidine derivatives as Src-family protein tyrosine kinase inhibitor compounds
INVENTOR(S): Armstrong, Helen M.; Beresis, Richard; Goulet, Joung L.; Holmes, Mark A.; Hong, Xingfang; Mills, Sander G.; Parsons, William H.; Sinclair, Peter J.; Steiner, Mark G.; Wong, Frederick; Zaller, Dennis M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 470 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000213	A1	20010104	WO 2000-US17443	20000626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206265	A1	20020522	EP 2000-941701	20000626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
US 6498165	B1	20021224	US 2000-604305	20000626

PRIORITY APPLN. INFO.: US 1999-141639P P 19990630
WO 2000-US17443 W 20000626

OTHER SOURCE(S): MARPAT 134:86271
GI



I

AB What are claimed are pyrimidine compds. (shown as I), or their pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers, and pharmaceutical compns. including the same and their use as inhibitors of tyrosine kinase enzymes and consequently their use in the prophylaxis and treatment of protein tyrosine kinase-assocd. disorders, such as immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to play a role, such as cancer, **angiogenesis**, atherosclerosis, graft rejection, rheumatoid arthritis and psoriasis. In I, R1, R2 = independently H, halo, OH, SH, CN, NO2, alkyl, alkoxy, acyloxy, alkoxycarbonyloxy, carbamoyloxy, alkylthio, sulfinyl, sulfonyl, acyl, alkoxycarbonyl, carbamoyl, amino, acylamino, ureido, sulfamoyl, sulfonylamino, or R1 and R2 can join together to form a fused methylenedioxy ring or a fused 6-membered arom. ring; terms such as 'alkyl' here and below are further defined in the claims. R3, R5 = independently H, C1-C6-alkyl unsubstituted or substituted with 1-3 substituents, aryl, or R3 and R5 taken together can represent :O; R3 or R5

can represent a 2 or 3 C methylene bridge forming a ring of 5-8 atoms fused to the A ring. R4 = H, C1-C6-alkyl, C1-C6-alkoxyl. X1, X2, X3, X4 in -X1:X2-X3:X4- are substituted or unsubstituted CH or N where 0-2 of X1, X2, X3, X4 are N. X5, X6 = independently N, C, optionally substituted CH. A ring = Ph, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, benzothienyl, benzofuranyl, indolyl, imidazolyl, benzimidazolyl, thiadiazolyl. R7, R8, R9, R10 = independently H, halo, OH, SH, CN, NO2, N3, N2+BF4-, alkyl, alkoxy, alkylthio, sulfinyl, sulfonyl, C1-C6-alkyl, C1-C6-perfluoroalkyl, acyl, alkoxycarbonyl, carbamoyl, acyloxy, alkoxycarbonyloxy, carbamoyloxy, amino, acylamino, ureido, sulfamoyl, sulfonylamino, two of R7, R8, R9, and R10 when on adjacent carbons join together to form a methylenedioxy bridge. N = 0-2. More than 500 example prepns. are given, but no preparative method is claimed and no data relating to the usefulness of the compds. are given.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 53 OF 54 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2000:814293 HCAPLUS
DOCUMENT NUMBER: 133:344620
TITLE: Use of **HMG-CoA** reductase inhibitors in the prevention of diseases whose pathogenesis is dependent on neovascularization
INVENTOR(S): Galper, Jonas B.; Kong, Dequan
PATENT ASSIGNEE(S): The Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067737	A2	20001116	WO 2000-US12309	20000505

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-132964P A2 19990507

AB **HMG-CoA** reductase inhibitors have a well-known mechanism in controlling cholesterol metab. **HMG-CoA** reductase inhibitors also have a less well-known effect on gene expression. The invention provides a new use for **HMG-CoA** reductase inhibitors in the treatment of diseases whose pathogenesis is dependent on neovascularization. **HMG-CoA** reductase inhibitors are administered at anti-angiogenic therapeutic doses for the treatment of primary and metastatic tumors, inflammatory processes involving new vessel formation, diabetic retinopathy, rheumatoid arthritis, and atherosclerosis. **HMG-CoA** reductase inhibitors affect the expression of genes through interference with the function of small GTP-binding proteins (e.g. Rho). Because of the low incidence of side effects with these agents, **HMG-CoA** reductase inhibitors could also be taken prophylactically to prevent the development of diseases in which the

pathogenesis is caused by neovascularization.

L10 ANSWER 54 OF 54 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 2000:670023 HCAPLUS
DOCUMENT NUMBER: 133:329364
TITLE: The **HMG-CoA** reductase inhibitor simvastatin activates the protein kinase Akt and promotes **angiogenesis** in normocholesterolemic animals
AUTHOR(S): Kureishi, Yasuko; Luo, Zhengyu; Shiojima, Ichiro; Bialik, Ann; Fulton, David; Lefer, David J.; Sessa, William C.; Walsh, Kenneth
CORPORATE SOURCE: Div. Cardiovascular Res., St. Elizabeth's Med. Cent., Boston, MA, 02136, USA
SOURCE: Nature Medicine (New York) (2000), 6(9), 1004-1010
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent studies suggest that statins can function to protect the vasculature in a manner that is independent of their lipid-lowering activity. We show here that statins rapidly activate the protein kinase Akt/PKB in endothelial cells. Accordingly, simvastatin enhanced phosphorylation of the endogenous Akt substrate endothelial nitric oxide synthase (eNOS), inhibited apoptosis and accelerated vascular structure formation in vitro in an Akt-dependent manner. Similar to vascular endothelial growth factor (VEGF) treatment, both simvastatin administration and enhanced Akt signaling in the endothelium promoted **angiogenesis** in ischemic limbs of normocholesterolemic rabbits. Therefore, activation of Akt represents a mechanism that can account for some of the beneficial side effects of statins, including the promotion of new blood vessel growth.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s rheumat?
L11 25842 RHEUMAT?

=> s l9 and l11
L12 26 L9 AND L11

=> d ibib abs 20-26

L12 ANSWER 20 OF 26 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 2002:256330 HCAPLUS
DOCUMENT NUMBER: 136:261827
TITLE: Method for the production of human antibodies, antibodies thus obtained and their use in therapy and diagnosis
INVENTOR(S): Opdenakker, Ghislain
PATENT ASSIGNEE(S): Rega Stichting Vzw, Belg.
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002026829	A1	20020404	WO 2001-EP11140	20010925

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001089930	A5	20020408	AU 2001-89930	20010925

PRIORITY APPLN. INFO.: EP 2000-203325 A 20000925
WO 2001-EP11140 W 20010925

AB The invention relates to a method for the prodn. of antimatter, in particular an antibody prepn., against an intraspecies or isospecies protein or peptide of interest, which method comprises detg. the presence of naturally occurring antimatter against an intraspecies or isospecies protein or peptide of interest or part thereof in the serum of a host; and selecting the B lymphocytes producing the antimatter against the protein or peptide of interest or part thereof to produce an antibody prepn. The invention discusses the use of antibodies in therapy for diseases characterized by overexpression of proteins, whereby the antibody inhibits the action of the protein.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 21 OF 26 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2002:86906 HCAPLUS
DOCUMENT NUMBER: 137:230547
TITLE: Hypothalamic digoxin related membrane Na+-K+ ATPase inhibition and familial basal ganglia calcification
AUTHOR(S): Kurup, Ravi Kumar; Kurup, Parameswara Achutha
CORPORATE SOURCE: Department of Neurology, Medical College Hospital, Trivandrum, Kerala, India
SOURCE: Neuroscience Research (Shannon, Ireland) (2002), 42(1), 35-44
CODEN: NERADN; ISSN: 0168-0102
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The isoprenoid pathway produces three key metabolites-digoxin (membrane sodium-potassium ATPase inhibitor and regulator of intracellular calcium-magnesium ratios), dolichol (regulator of N-glycosylation of proteins) and ubiquinone (free radical scavenger). The pathway was assessed in a rare and specific type of familial basal ganglia calcification that is described. The family had a coexistence of basal ganglia calcification (six out of 10 cases), schizophrenia, Parkinson's disease, Alzheimer's disease, **rheumatoid** arthritis, systemic tumors and syndrome X and were all right hemispheric dominant. The isoprenoid pathway was also studied for comparison in right hemispheric dominant, bihemispheric dominant and left hemispheric dominant individuals. The isoprenoid pathway was upregulated with increased digoxin synthesis in familial basal ganglia calcification. Membrane sodium-potassium ATPase inhibition can lead to an increase in intracellular calcium and calcification of the basal ganglia. There was an increase in tryptophan catabolites and a redn. in tyrosine catabolites. There was also an increase in dolichol and glycoconjugate levels with reduced lysosomal

stability in these patients. The ubiquinone levels were low, and free radical levels increased. The cholesterol-phospholipid ratio was increased and the glycoconjugate level of the erythrocyte membrane reduced in this group of patients. No significance difference was noted in family members with and without basal ganglia calcification. These findings were correlated with the pathogenesis of syndrome X, immune mediated diseases, degenerations, tumors and psychiatric disorders noted in the familial basal ganglia calcification described. The biochem. patterns obtained in familial basal ganglia calcification correlated with those in right hemispheric dominance.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

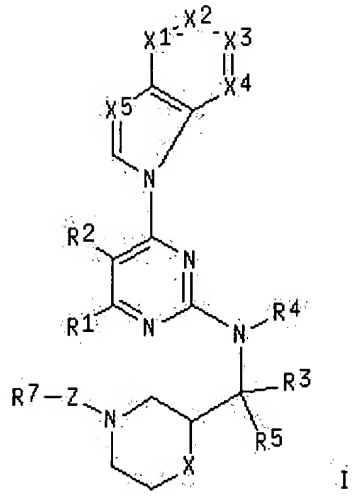
L12 ANSWER 22 OF 26 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2001:12274 HCAPLUS
DOCUMENT NUMBER: 134:86272
TITLE: Preparation of pyrimidine derivatives as Src-family protein tyrosine kinase inhibitor compounds
INVENTOR(S): Hunt, Julianne A.; Mills, Sander G.; Sinclair, Peter J.; Zaller, Dennis M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 181 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000214	A1	20010104	WO 2000-US17472	20000626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6316444	B1	20011113	US 2000-603699	20000626
EP 1194152	A1	20020410	EP 2000-944858	20000626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003503354	T2	20030128	JP 2001-505923	20000626

PRIORITY APPLN. INFO.: US 1999-141597P P 19990630
WO 2000-US17472 W 20000626

OTHER SOURCE(S): MARPAT 134:86272
GI



I

AB What are claimed are pyrimidine compds. (shown as I), or their pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers, and pharmaceutical compns. including the same and their use as inhibitors of tyrosine kinase enzymes and consequently their use in the prophylaxis and treatment of protein tyrosine kinase-assocd. disorders, such as immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to play a role, such as cancer, angiogenesis, atherosclerosis, graft rejection, **rheumatoid** arthritis and psoriasis. In I, R1, R2 = independently H, halo, OH, SH, CN, NO2, alkyl, alkoxy, acyloxy, alkoxycarbonyloxy, carbamoyloxy, alkylthio, sulfinyl, sulfonyl, acyl, alkoxycarbonyl, carbamoyl, amino, acylamino, alkoxycarbonylamino, ureido, sulfamoyl, sulfonylamino, or R1 and R2 can join together to form a fused methylenedioxy ring or a fused 6-membered arom. ring; terms such as 'alkyl' here and below are further defined in the claims. R3, R5 = independently H, C1-C6-alkyl unsubstituted or substituted with 1-3 substituents, aryl (Ph or naphthyl unsubstituted or substituted with 1-3 substituents), or R3 and R5 taken together can represent :O. R4 = H, C1-C6-alkyl, C1-C6-alkoxyl, or R4 and X can join together to form a 5- or 6-membered ring with substituted methylene or ethylene. X1, X2, X3, X4 in -X1:X2-X3:X4- are substituted CH or N where 0-2 of X1, X2, X3, X4 are N. X5 = N, CH. R7 = H, alkyl, alkoxy, amino. X = O, S, SO, SO2, imino. Z = C:O, SO2, substituted P(:O)(OH) or a single bond. 44 Example prepns. are given, but no preparative method is claimed and no data relating to the usefulness of the compds. are given.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 23 OF 26 HCAPLUS COPYRIGHT 2003 ACS
Full Text

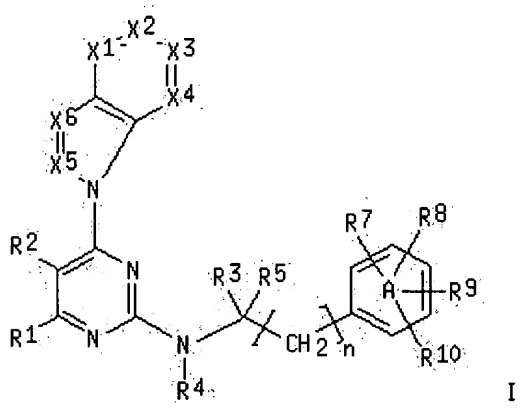
ACCESSION NUMBER: 2001:12273 HCAPLUS
DOCUMENT NUMBER: 134:86271
TITLE: Preparation of pyrimidine derivatives as Src-family protein tyrosine kinase inhibitor compounds
INVENTOR(S): Armstrong, Helen M.; Beresis, Richard; Goulet, Joung L.; Holmes, Mark A.; Hong, Xingfang; Mills, Sander G.; Parsons, William H.; Sinclair, Peter J.; Steiner, Mark G.; Wong, Frederick; Zaller, Dennis M.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 470 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000213	A1	20010104	WO 2000-US17443	20000626
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206265	A1	20020522	EP 2000-941701	20000626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
US 6498165	B1	20021224	US 2000-604305	20000626

PRIORITY APPLN. INFO.: US 1999-141639P P 19990630
WO 2000-US17443 W 20000626

OTHER SOURCE(S): MARPAT 134:86271
GI



I

AB What are claimed are pyrimidine compds. (shown as I), or their pharmaceutically acceptable salts, hydrates, solvates, crystal forms and individual diastereomers, and pharmaceutical compns. including the same and their use as inhibitors of tyrosine kinase enzymes and consequently their use in the prophylaxis and treatment of protein tyrosine kinase-assocd. disorders, such as immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to play a role, such as cancer, angiogenesis, atherosclerosis, graft rejection, **rheumatoid** arthritis and psoriasis. In I, R1, R2 = independently H, halo, OH, SH, CN, NO2, alkyl, alkoxy, acyloxy, alkoxycarbonyloxy, carbamoyloxy, alkylthio, sulfinyl, sulfonyl, acyl, alkoxycarbonyl, carbamoyl, amino, acylamino, ureido, sulfamoyl, sulfonylamino, or R1 and R2 can join together to form a fused methylenedioxy ring or a fused 6-membered arom. ring; terms such as 'alkyl' here and below are further defined in the claims. R3, R5 = independently H, C1-C6-alkyl unsubstituted or substituted with 1-3 substituents, aryl, or R3 and R5 taken together can represent :O; R3 or R5

can represent a 2 or 3 C methylene bridge forming a ring of 5-8 atoms fused to the A ring. R4 = H, C1-C6-alkyl, C1-C6-alkoxyl. X1, X2, X3, X4 in -X1:X2-X3:X4- are substituted or unsubstituted CH or N where 0-2 of X1, X2, X3, X4 are N. X5, X6 = independently N, C, optionally substituted CH. A ring = Ph, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, benzothienyl, benzofuranyl, indolyl, imidazolyl, benzimidazolyl, thiadiazolyl. R7, R8, R9, R10 = independently H, halo, OH, SH, CN, NO2, N3, N2+BF4-, alkyl, alkoxy, alkylthio, sulfinyl, sulfonyl, C1-C6-alkyl, C1-C6-perfluoroalkyl, acyl, alkoxycarbonyl, carbamoyl, acyloxy, alkoxycarbonyloxy, carbamoyloxy, amino, acylamino, ureido, sulfamoyl, sulfonylamino, two of R7, R8, R9, and R10 when on adjacent carbons join together to form a methylenedioxy bridge. N = 0-2. More than 500 example prepns. are given, but no preparative method is claimed and no data relating to the usefulness of the compds. are given.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 24 OF 26 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2000:814293 HCAPLUS
DOCUMENT NUMBER: 133:344620
TITLE: Use of **HMG-CoA** reductase inhibitors in the prevention of diseases whose pathogenesis is dependent on neovascularization
INVENTOR(S): Galper, Jonas B.; Kong, Dequan
PATENT ASSIGNEE(S): The Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067737	A2	20001116	WO 2000-US12309	20000505

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-132964P A2 19990507

AB **HMG-CoA** reductase inhibitors have a well-known mechanism in controlling cholesterol metab. **HMG-CoA** reductase inhibitors also have a less well-known effect on gene expression. The invention provides a new use for **HMG-CoA** reductase inhibitors in the treatment of diseases whose pathogenesis is dependent on neovascularization. **HMG-CoA** reductase inhibitors are administered at anti-angiogenic therapeutic doses for the treatment of primary and metastatic tumors, inflammatory processes involving new vessel formation, diabetic retinopathy, **rheumatoid** arthritis, and atherosclerosis. **HMG-CoA** reductase inhibitors affect the expression of genes through interference with the function of small GTP-binding proteins (e.g. Rho). Because of the low incidence of side effects with these agents, **HMG-CoA** reductase inhibitors could also be taken prophylactically to prevent the development of diseases in which the

pathogenesis is caused by neovascularization.

L12 ANSWER 25 OF 26 HCAPLUS COPYRIGHT 2003 ACS
Full Text

ACCESSION NUMBER: 2000:645885 HCAPLUS
DOCUMENT NUMBER: 133:217694
TITLE: Endotoxin-modulating compounds for therapy of heart failure and cachexia
INVENTOR(S): Anker, Stefan; Coats, Andrew; Volk, Hans-Dieter; Rauchhaus, Mathias; Schumann, Ralf Reiner
PATENT ASSIGNEE(S): Max-Delbruck-Centrum fur Molekulare Medizin, Germany
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000053224	A2	20000914	WO 2000-EP2299	20000309
WO 2000053224	A3	20020404		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1212064	A2	20020612	EP 2000-920504	20000309
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.:

GB 1999-5300	A	19990309
GB 1999-5307	A	19990309
GB 1999-5310	A	19990309
GB 1999-5314	A	19990309
GB 1999-5315	A	19990309
WO 2000-EP2299	W	20000309

AB A method of treating, preventing or ameliorating chronic or acute heart failure in a patient comprises administering to the patient an effective amt. of a compd. that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids, or an antibody capable of binding LPS, a compd. that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin (lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. A method of treating, preventing or ameliorating endotoxin-mediated immune activation in acute or chronic heart failure in a patient comprises administering to the patient an effective amt. of a compd. that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol., e.g. LPS binding protein, BPI, lipoproteins, bile acids or an antibody capable of binding LPS, a compd. that is able to bind to an endotoxin (lipopolysaccharide; LPS) mol. or bacterium in the gut, e.g. charcoal, a bile acid or Fuller's earth, an antibacterial agent that is substantially active in the gut, an agent that is able to inhibit the response by a cell to endotoxin

(lipopolysaccharide; LPS), an agent that may form a barrier or that otherwise impedes translocation of bacteria or endotoxin (LPS) from the gut into the patient's circulation. Also disclosed is a method for treating cachexia and wasting syndromes due to diseases other than congestive heart failure.

L12 ANSWER 26 OF 26 HCAPLUS COPYRIGHT 2003 ACS
Full Text
ACCESSION NUMBER: 1993:552113 HCAPLUS
DOCUMENT NUMBER: 119:152113
TITLE: Tocotrienols and tocotrienol-like compounds and methods for their use
INVENTOR(S): Lane, Ronald H.; Qureshi, Asaf A.; Salser, Winston A.
PATENT ASSIGNEE(S): Lipogenics, Inc., USA
SOURCE: Eur. Pat. Appl., 62 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 543417	A1	19930526	EP 1992-119840	19921120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 2000169369	A2	20000620	JP 1999-332117	19921120
CN 1073357	A	19930623	CN 1992-111842	19921121
US 5919818	A	19990706	US 1997-991912	19971216
US 6143770	A	20001107	US 1998-182531	19981028
US 6204290	B1	20010320	US 1998-182384	19981028

PRIORITY APPLN. INFO.:
US 1991-796486 A 19911122
JP 1992-509587 A3 19921120
US 1996-719284 A1 19960924
US 1997-991912 A1 19971216

OTHER SOURCE(S): MARPAT 119:152113

AB Tocotrienols and tocotrienol-like compds. displaying biol. activity are disclosed. The compds. may be obtained from biol. sources or by chem. synthesis; they may be used in pharmaceutical compns., foodstuffs, and dietary supplements. The compds., and mixts thereof, may be used as hypocholesteremic, antithrombotic, antioxidizing, antiatherogenic, antiinflammatory, and immunoregulatory agents, or as agents to decrease lipoprotein (a) concn. in the blood or to increase feed conversion efficiency. Several of the compds. of the invention were isolated from rice bran (structures and spectral data included). Effects on antibody titers, on inhibition of superoxide release, on levels of cholesterol (total cholesterol, HDL-cholesterol, LDL-cholesterol), on **HMG-CoA** reductase, etc. are reported.

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	105.47	112.38

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-16.28	-16.28

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS,

BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 10:39:46 ON 09 JUL 2003

67 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> d his

(FILE 'HOME' ENTERED AT 10:26:19 ON 09 JUL 2003)

FILE 'REGISTRY' ENTERED AT 10:26:42 ON 09 JUL 2003
L1 1 S ATORVASTATIN/CN
L2 18 S 134523-00-5/RN OR 134523-00-5/CRN

FILE 'HCAPLUS' ENTERED AT 10:27:48 ON 09 JUL 2003
L3 875 S L2
L4 17678 S ANGIOGENES?
L5 14 S L3 AND L4
L6 43657 S ATHEROSCLER? OR ARTERIOSCLER?
L7 191 S L6 AND L3
L8 34 S L3 (S) L6
L9 4737 S HMG-COA
L10 54 S L9 AND L4
L11 25842 S RHEUMAT?
L12 26 S L9 AND L11

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 10:39:46 ON 09 JUL 2003

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13 FILE ADISCTI
5 FILE ADISINSIGHT
7 FILE ADISNEWS
11 FILE BIOSIS
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11 FILES SEARCHED...
1 FILE CANCERLIT
26 FILE CAPLUS
18 FILE DDFU
4 FILE DRUGNL
21 FILE DRUGU
29 FILES SEARCHED...
4 FILE EMBASE
1 FILE ESBIOBASE
1 FILE FEDRIP
1 FILE GENBANK
21 FILE IFIPAT
3 FILE MEDLINE
1 FILE PASCAL
12 FILE PHARMAML
20 FILE PHIN
32 FILE PROMT
58 FILES SEARCHED...

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          6   FILE SCISEARCH
         13   FILE TOXCENTER
        356   FILE USPATFULL
         36   FILE USPAT2
         59   FILE WPIDS
         59   FILE WPINDEX

  27 FILES HAVE ONE OR MORE ANSWERS,   67 FILES SEARCHED IN STNINDEX

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  18 FILES HAVE ONE OR MORE ANSWERS,   67 FILES SEARCHED IN STNINDEX

L14  QUE L13 NOT PY>1999

=> rank
THIS COMMAND IS NOT AVAILABLE IN STNINDEX
Enter HELP COMMANDS at an arrow prompt (=>) for a list of commands
that may be used in STNINDEX.

=> help commands
Enter one of these commands at the arrow prompt (=>).

ACTIVATE ----- Assign L#s to saved query or answer set.
DELETE ------- Delete saved or current session items.
DISPLAY ------ Display saved or current session items.
DUPLICATE ---- Determine duplicate answers
EDIT --------- Modify the text of an E-number entry.
EXPAND ------- Look at the index around a term.
FILE --------- Specify the search and display file.
HELP --------- For help on how to use the system.
INDEX -------- Specify the Index environment.
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LOGOFF ------- End the online session.
NEWS --------- Display current news about the system.
SAVE --------- Save an L-numbered query or answer set.
SEARCH ------- Perform a search.
SET ---------- Set terminal and interaction options.
? ------------ The same as HELP.
Enter one of these commands at the arrow prompt (=>).


For more detailed information about a command, enter HELP followed by
the command name at an arrow prompt.

Example: => HELP SEARCH

For information on entering multiple commands at a single arrow
prompt, enter HELP COMMAND STACKING.

=> d rank
F1          47   USPATFULL
F2          26   PROMT
F3          17   PHIN
F4          11   PHARMAML
F5           8   DRUGU
F6           7   ADISCTI
F7           5   DDFU
F8           5*  ADISINSIGHT
F9           4   DRUGNL
F10          3   TOXCENTER
F11          2   ADISNEWS
F12          2   EMBASE
F13          2   SCISEARCH
F14          1   BIOSIS
F15          1   MEDLINE
F16          1   WPIDS
F17          1   WPINDEX
F18          1*  FEDRIP


=> file f1-6
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               6.05     118.43

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                 ENTRY    SESSION
CA SUBSCRIBER PRICE                               0.00     -16.28

FILE 'USPATFULL' ENTERED AT 10:46:34 ON 09 JUL 2003
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FILE 'PROMT' ENTERED AT 10:46:34 ON 09 JUL 2003
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FILE 'PHIN' ENTERED AT 10:46:34 ON 09 JUL 2003
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FILE 'DRUGU' ENTERED AT 10:46:34 ON 09 JUL 2003
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FILE 'ADISCTI' ENTERED AT 10:46:34 ON 09 JUL 2003

=> s l14
L15 116 L14

=> dup rem
ENTER L# LIST OR (END):l15
DUPLICATE IS NOT AVAILABLE IN 'PHARMAML'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L15
L16 115 DUP REM L15 (1 DUPLICATE REMOVED)

=> s lovastatin and l16
L17 31 LOVASTATIN AND L16

=> d 30-31

L17 ANSWER 30 OF 31 ADISCTI
Full Text
AN 1993:30653 ADISCTI
DN 800235323
TI **Rheumatic** manifestations of hyperlipidemia and antihyperlipidemia drug therapy.
AU Careless D J; Cohen M G.
SO Seminars in Arthritis and Rheumatism (Oct 1, 1993), Vol. 23, pp. 90-98
DT Citation
RE Hyperlipidaemia| Rheumatic Disease
FS Citation
LA English

L17 ANSWER 31 OF 31 ADISCTI
Full Text
AN 1991:46264 ADISCTI
DN 800092421
TI **Lovastatin**-induced lupus erythematosus.
ADIS TITLE: **Lovastatin**: adverse reactions.
Systemic lupus erythematosus.
AU Ahmad S.
CS Cardio-Diagnostic Clinique, Fairmont, West Virginia, USA.
SO Archives of Internal Medicine (Aug 1, 1991), Vol. 151, pp. 1667-1668
DT Case
RE Hyperlipidaemia
FS Summary
LA English
WC 174

=> d ibib abs 26-29

L17 ANSWER 26 OF 31 DRUGU
Full Text
ACCESSION NUMBER: 1997-45858 DRUGU T S
TITLE: Occurrence of polymyalgia **rheumatica** under medication with **HMG-COA**-reductase inhibitor (**lovastatin**).
AUTHOR: Schmidt W A; Hug A M; Luebke H J; Brockhaus E; Gromnica Ihle E
LOCATION: Berlin, Ger.

SOURCE: Z.Rheumatol. (56, Suppl. 1, 52, 1997)
CODEN: ZRHMBQ ISSN: 0340-1855
AVAIL. OF DOC.: Rheumaklinik Berlin-Buch, Germany.
LANGUAGE: German
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1997-45858 DRUGU T S
AB A case of polymyalgia **rheumatica** 3 mth after starting **lovastatin** (Mevinacor, Merck-USA) treatment is reported in an elderly man with hypercholesterolemia who had suffered an MI and was also receiving aspirin, isosorbide mononitrate and diltiazem. Symptoms regressed within 48 hr of prednylidene. **Lovastatin** was withdrawn but symptoms recurred when a trial discontinuation of the glucocorticoid was undertaken 6 wk later. 9 Mth after the onset of the polymyalgia **rheumatica**, low dose prednisolone was still required because ESR remained elevated despite disappearance of clinical symptoms. A causal link between **lovastatin** and the polymyalgia **rheumatica** is possible, but not certain. (conference abstract).
ABEX A 76 yr-old man with hypercholesterolemia started **lovastatin** 20 mg/day in mid-April 1996 in addition to treatment, begun 4 yr earlier, with aspirin 100 mg, isosorbide mononitrate 60 mg and diltiazem 180 mg following an MI. At the start of July 1996, he developed pain, initially in the pelvic, later in the shoulder region. 2 Wk later, **lovastatin** was withdrawn and he was hospitalized 14 days later. He complained of morning stiffness, lasting 2 hr and was depressed. ESR and C-reactive protein were elevated, but body weight was constant, and vision and temporal arteries were normal, **Rheumatic** symptoms regressed within 48 hr of giving prednylidene (36 mg initially) but recurred on trial withdrawal of the steroid 6 wk later, when ESR rose once more. 9 Mth after the initial symptoms, the patients was clinically asymptomatic under prednisolone, 5 mg/day, but ESR was 30 mm/hr. (S54/JC) Aufreten einer polymyalgia **rheumatica** unter medikation mit **HMG-CoA**-reduktase-hemmer (**lovastatin**).

L17 ANSWER 27 OF 31 DRUGU COPYRIGHT 2003 THOMSON DERWENT
Full Text
ACCESSION NUMBER: 1993-14959 DRUGU C T S E
TITLE: The Cortisone Era: Aspects of Its Impact. Some Contributions of the Merck Laboratories.
AUTHOR: Hirschmann R
LOCATION: Philadelphia, Pennsylvania, United States
SOURCE: Steroids (57, No. 12, 579-92, 1992) 31 Fig. 158 Ref.
CODEN: STEDAM ISSN: 0039-128X
AVAIL. OF DOC.: Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature
AN 1993-14959 DRUGU C T S E
AB The development of steroid synthesis is reviewed, with special reference to cortisone. Synthesis of equilenin, estrone, dehydrocorticosterone, cortisone-acetate and cortisol (hydrocortisone) is discussed.The search for alternative routes, total syntheses, the impact of structural thinking and the biological lessons of this research are considered. The development of 2nd generation compounds such as prednisolone, methylprednisolone, isoflupredone, cortexone, fludrocortisone, dexamethasone and betamethasone is discussed. Structure activity relationships and drug design are considered and the development of

prodrugs (prednisolone-phosphate) is mentioned. Other drug developed as a consequence of steroid research include mifepristone, **lovastatin** and finasteride.

ABEX Attempts to synthesize cortisone were initiated following the discovery of its effects on patients with **rheumatoid** arthritis. Equilenin and estrone had already been synthesized and this work had laid down the foundations for future research. Cortisone-acetate was 1st synthesized from deoxycholic acid in a 37 step process, and 4 yr later a scaled up synthesis had been developed. Research indicated that cortisol was the active hormone and by 1950 chemists had managed to synthesize it. Alternative methods of synthesis including microbial transformation have been investigated, and methods for total syntheses have been developed. Clinical experience with cortisone and cortisol led to the realization that physiological doses of steroids cause side-effects. This is due to the multiple effects of cortisol, other than its antiinflammatory effects. Isolation of aldosterone provided proof that glucocorticoid and mineralocorticoid activities are mediated by different receptors. Second generation steroids include prednisolone, methylprednisolone, isoflupredone, cortexone, fludrocortisone, dexamethasone and betamethasone. Development of 21-phosphate prodrugs (prednisolone-phosphate, cortisone-phosphate) is described. Other drugs that have been developed as a consequence of steroid research include the progesterone antagonist mifepristone, the **HMG-CoA** inhibitor **lovastatin** and the androgen antagonist finasteride. (TOB)

L17 ANSWER 28 OF 31 ADISCTI COPYRIGHT (C) 2003 Adis Data Information BV
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ACCESSION NUMBER: 1997:14254 ADISCTI
DOCUMENT NUMBER: 800549056
TITLE: **Lovastatin**-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin.
ADIS TITLE: **Lovastatin** + clarithromycin, azithromycin: drug interactions (serious).
Rhabdomyolysis (first report).
AUTHOR: Grunden J W; Fisher K A.
CORPORATE SOURCE: Ferris State University, Kalamazoo, Michigan, USA.
SOURCE: Annals of Pharmacotherapy (Aug 1, 1997), Vol. 31, pp. 859-863
DOCUMENT TYPE: Case
REFERENCE: Antibacterials| Hyperlipidaemia
FILE SEGMENT: Summary
LANGUAGE: English
WORD COUNT: 518

L17 ANSWER 29 OF 31 ADISCTI COPYRIGHT (C) 2003 Adis Data Information BV
Full Text

ACCESSION NUMBER: 1994:49462 ADISCTI
DOCUMENT NUMBER: 800319858
TITLE: Recurrent hyperthermia due to **lovastatin**.
ADIS TITLE: **Lovastatin**: adverse reactions (serious).
Recurrent hyperthermia (first report).
AUTHOR: Von Pohle W R.
CORPORATE SOURCE: Loma Linda University School of Medicine, Loma Linda, California, USA.
SOURCE: Western Journal of Medicine (Oct 1, 1994), Vol. 161, pp. 427-428
DOCUMENT TYPE: Case
REFERENCE: Hyperlipidaemia
FILE SEGMENT: Summary
LANGUAGE: English

WORD COUNT: 250

=> d ibib abs 20-25

L17 ANSWER 20 OF 31 PHIN COPYRIGHT 2003 PJB
Full Text

ACCESSION NUMBER: 88:8740 PHIN
DOCUMENT NUMBER: S00155808
DATA ENTRY DATE: 18 Apr 1988
TITLE: British Bio-technology's expansion plans
SOURCE: Scrip (1988) No. 1302 p10
DOCUMENT TYPE: Newsletter
FILE SEGMENT: FULL

L17 ANSWER 21 OF 31 PHIN COPYRIGHT 2003 PJB
Full Text

ACCESSION NUMBER: 87:16445 PHIN
DOCUMENT NUMBER: S00141824
DATA ENTRY DATE: 4 Dec 1987
TITLE: Antioxidants and atherosclerosis
SOURCE: Scrip (1987) No. 1265 p23
DOCUMENT TYPE: Newsletter
FILE SEGMENT: FULL

L17 ANSWER 22 OF 31 PHIN COPYRIGHT 2003 PJB
Full Text

ACCESSION NUMBER: 87:15634 PHIN
DOCUMENT NUMBER: S00143144
DATA ENTRY DATE: 22 Dec 1987
TITLE: Products in 1988 and beyond
SOURCE: Scrip (1987) No. 1270 p17
DOCUMENT TYPE: Newsletter
FILE SEGMENT: FULL

L17 ANSWER 23 OF 31 PHIN COPYRIGHT 2003 PJB
Full Text

ACCESSION NUMBER: 86:13391 PHIN
DOCUMENT NUMBER: S00101671
DATA ENTRY DATE: 3 Dec 1986
TITLE: New UK biotechnology company
SOURCE: Scrip (1986) No. 1162 p7
DOCUMENT TYPE: Newsletter
FILE SEGMENT: FULL

L17 ANSWER 24 OF 31 PHIN COPYRIGHT 2003 PJB
Full Text

ACCESSION NUMBER: 86:13036 PHIN
DOCUMENT NUMBER: S00102047
DATA ENTRY DATE: 10 Dec 1986
TITLE: Products in the news in 1986
SOURCE: Scrip (1986) No. 1166/7 p11
DOCUMENT TYPE: Newsletter
FILE SEGMENT: FULL

L17 ANSWER 25 OF 31 PHARMAML COPYRIGHT 2003 MARKETLETTER
Full Text

ACCESSION NUMBER: 1625539 PHARMAML
TITLE: Hoechst Streamlines R&D: Update On Early Pipeline
SOURCE: Marketletter October 10, 1994
DOCUMENT TYPE: Newsletter
WORD COUNT: 1270

TX As the costs of R&D around the world have soared at "an alarming rate" the introduction of new active substances has been stagnating for years, according to Jurgen Reden, head of pharmaceutical research at the German chemical and pharmaceutical company, Hoechst.

R&D costs of the Hoechst group, however, will be slightly lower this year, between 3% and 4%, than the 1.6 billion Deutschemarks ($1 billion) spent on R&D in 1993, said Dr Reden at the group's recent pharmaceutical meeting in Frankfurt, Germany (see also Marketletter October 3). A further reduction of around 10% is planned for 1995.

The group has been restructuring its R&D operations over the past couple of years to introduce organizational changes that it hopes will bring a higher success rate and greater efficiency. The responsibilities for research, preclinical development and clinical development have been separated, and the creation of strategic business units, which are responsible for the individual therapeutic areas and comprise all the required disciplines, has led to a qualitative improvement in research projects, said Dr Reden.

This process, which Dr Reden says is not over yet, has led to a portfolio which is centered on six therapeutic areas: cardiovascular disease, infections, metabolic disorders, the central nervous system, **rheumatism**/immunology and endocrinology. Hoechst's target is to develop products that will have the potential to generate (peak) sales of around 500 million marks annually, with the exception of drugs that are potential treatments of AIDS. The company's near-term pipeline was reviewed in last week's issue of the Marketletter.

Hoechst has advanced three of its new agents into Phase I clinical development. The first of these is Hoe 642, which has entered Phase I clinical trials and may be of use in the treatment of life-threatening cardiac arrhythmias and other cardiac applications. Dr Reden said that this is the lead agent in a program which is involved in the development of agents which can inhibit cell sodium/hydrogen exchange. "When subjected to a lack of oxygen, the stimulation of this system quickly leads to cardiac arrhythmias and causes the heart muscle to cramp and die," said Dr Reden.

In ischemic conditions, cardiac muscle cells enter anaerobic metabolism, which involves the generation of protons (H+ ions), the activation of the Na+/H+ exchanger and the consumption of ATP. Within about 20 minutes, calcium influx into the hypoxic cell causes arrhythmias and cell death. Furthermore, after reperfusion of the heart muscle (eg after thrombolysis in cases of acute myocardial infarction), high levels of intracellular sodium and calcium causes reperfusion arrhythmias and further contributes to cardiac muscle cell death at the affected site.

By interrupting the action of the H+/Na+ exchanger with Hoe 642, the pH of the hypoxic cells is reduced, which leads to inactivation of ATP-hydrolysis, a process known as acid-freezing. This conserves the cell in an "inactive" state and stops calcium and sodium build-up, allowing slow return to normal cell function after reperfusion.

Hoechst anticipates that potential indications for Hoe 642 may be acute myocardial infarction, cardiac surgery and transplantation, percutaneous transluminal coronary angioplasty and in the treatment of arrhythmias and angina pectoris attacks. Dr Reden also said that the company has identified a series of promising reference compounds from the sulfonylurea class, which may be of use in preventing sudden cardiac death.

In the field of anti-infectives, Dr Reden said that Hoechst is progressing well with its anti-AIDS project, which it is conducting in collaboration with Bayer. The collaboration has identified a lead candidate compound, but the company was reluctant to discuss details of this before initial clinical data become available at the end of the year. The new agent is being tested for tolerability in healthy volunteers; Phase I studies started in August. Bayer has also expressed reluctance to raising premature hopes in this area, and Bayer chairman Manfred Schneider recently said that "the earliest we can contemplate a drug in this area will be at the turn of the century."
Dr Reden added that Hoechst is also in the midst of discussions with an unnamed Californian gene therapy company in the area of HIV treatment. Antibacterial research is concentrated at Roussel Uclaf's facilities in Paris, France, and the highest priority project, which is still at an early stage, is a new macrolide with an interesting activity profile, he said.

Metabolic Research The metabolic diseases research has provided the other new agent to reach clinical trials, Hoe 901. This drug is a variation on insulin which exhibits a long-lasting, even effect which prevents sharp fluctuations in the blood sugar level of type I diabetic patients, thereby improving their quality of life and (hopefully) preventing some of the long-term implications of the disease. The insulin analog has been developed by substituting amino acids in the insulin polypeptide chains.

The diabetes project has also afforded some promising leads in type II diabetic patients, said Dr Reden. Primary objectives in the management of this condition are the control of insulin resistance in the muscular and fatty tissues and preventing pathologically elevated glucose production in the liver, either released from glycogen or from gluconeogenesis. These two processes have a common intermediate step, the production of glucose-6-phosphate which is converted into glucose in the final step of the pathway. Hoechst aims to develop inhibitors of this final step, targeting the enzyme glucose-6-phosphatase. Following further optimization, the company hopes to be able to take a candidate into development at the beginning of next year.

One of the other targets of Hoechst's metabolic disease program is arteriosclerosis. Different mechanisms are involved in the formation of the atherosclerotic plaque, said Dr Reden, including cellular changes, build-up of lipoproteins in the arterial walls and coagulatory processes on the surface of the endothelium.

The metabolism group are fixing their attentions on new ways of regulating blood cholesterol levels. Apart from the inhibition of cholesterol biosynthesis (a process targeted by **HMG-CoA** reductase inhibitors such as **lovastatin** and simvastatin), there is the possibility of stimulating the formation of low-density lipoprotein receptors. This approach enables larger quantities of LDL (known to be a risk factor in cv disease) to be absorbed by the cells and removed from the blood. Hoechst has identified a lead compound in this area and

entered it into preclinical development at the start of the year.

Hoechst's CNS research is focused on two diseases, Alzheimer's and schizophrenia. Besipirdine and propentofylline, the company's lead products in AD and dementia, were dealt with in last week's issue. More than half of the funding in this area is concentrating on agents which inhibit the aggregation of beta amyloid and the avoidance of its toxic effects on neurons.

The main project being worked on by the **rheumatology** unit is the development of leflunomide for **rheumatoid** arthritis (Marketletters passim). Roussel Uclaf is developing HR 325, a follow-on compound with a different profile, and also has an agreement with Vertex concerning interleukin-2 convertase inhibitors for RA. Because of this, Hoechst has decided to focus its efforts in the area of osteoarthritis. The company is looking for substances that are capable of accelerating aggrecan synthesis (a component of the cartilage matrix), or inhibiting/compensating for the cytokine-induced degradation of this substance. This project is very much still at the basic research stage.

Finally, Dr Reden turned to a relatively new area of research for Hoechst, bone disorders. The company is collaborating with Hoechst Japan and Roussel Uclaf in this project. A variety of approaches are being assessed, including hormone control, inhibition of bone resorption and stimulating bone formation. In Japan, a bisphosphonate to prevent bone resorption is in clinical trials, and a bone growth factor is in the early stages of characterization and pharmacological evaluation.

=> d ti 1-19

L17 ANSWER 1 OF 31 USPATFULL
TI Spiro-substituted azacycles as modulators of chemokine receptor activity

L17 ANSWER 2 OF 31 USPATFULL
TI Tocotrienols and tocotrienol-like compounds and methods for their use

L17 ANSWER 3 OF 31 USPATFULL
TI Substituted aminoquinolines as modulators of chemokine receptor activity

L17 ANSWER 4 OF 31 USPATFULL
TI Prevention of atherosclerosis using NADPH oxidase inhibitors

L17 ANSWER 5 OF 31 USPATFULL
TI Compositions and methods for treating and preventing pathologies including cancer

L17 ANSWER 6 OF 31 USPATFULL
TI Phenylacetate and derivatives alone or in combination with other compounds against neoplastic conditions and other disorders

L17 ANSWER 7 OF 31 USPATFULL
TI Cell differentiation induction with mevalonate and mevalonolactone derivatives

L17 ANSWER 8 OF 31 USPATFULL
TI Compositions and methods for treating and preventing pathologies including cancer

L17 ANSWER 9 OF 31 USPATFULL

TI Tocotrienols and tocotrienol-like compounds and methods for their use

L17 ANSWER 10 OF 31 USPATFULL
TI Cell differentiation induction with mevalonate and mevalonolactone derivatives

L17 ANSWER 11 OF 31 USPATFULL
TI Prevention of atherosclerosis using NADPH oxidase inhibitors

L17 ANSWER 12 OF 31 USPATFULL
TI Compositions and methods for treating and preventing pathologies including cancer

L17 ANSWER 13 OF 31 USPATFULL
TI Tocotrienols and tocotrienol-like compounds and methods for their use

L17 ANSWER 14 OF 31 USPATFULL
TI Inhibitors of prenyl-protein transferases

L17 ANSWER 15 OF 31 PROMT COPYRIGHT 2003 Gale Group

TI Follow-Up Data From Landmark Cholesterol Study Indicate Life-Saving Benefits of Zocor(R) Are Maintained.

L17 ANSWER 16 OF 31 PROMT COPYRIGHT 2003 Gale Group

TI /FIRST AND FINAL ADD -- PHTH014 -- Merck & Co., Inc./.

L17 ANSWER 17 OF 31 PROMT COPYRIGHT 2003 Gale Group

TI R&D Perspectives from Kamakura (4) Part I

L17 ANSWER 18 OF 31 PROMT COPYRIGHT 2003 Gale Group

TI Hoechst Streamlines R&D: Update On Early Pipeline

L17 ANSWER 19 OF 31 PHIN COPYRIGHT 2003 PJB

TI British Bio-technology looks for pharmaceutical niche

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CA SUBSCRIBER PRICE	0.00	-16.28

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